Deliverable 4.2

Report on guidelines implementation

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1-Background and rationale

1.1 Rare diseases guidelines implementation: gaps and needs

"There is probably no other area in public health in which 27 national approaches could be considered to be so inefficient and ineffective as with rare diseases (RD). The reduced number of patients for these diseases and the need to mobilise resources could be only efficient if done in a coordinated European way." – European Commission COUNCIL RECOMMENDATION of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02).

It is well known that the field of RD suffers from a shortage of medical and scientific knowledge. For a long time, doctors, researchers and policy makers were unaware of RD and until very recently there was no real research or public health policy concerning issues related to the field. There is no cure for most of RD, but the appropriate treatment and medical care can improve the quality of life of those affected and extend their life expectancy.

Clinical Practice Guidelines (CPGs) have been developed during last decades to assist practitioners and patient decisions about appropriate healthcare for specific conditions, however, given the low prevalence of RD, few of them have been addressed to the management of these conditions. Despite the efforts performed in the last years to increase the number of CPGs covering RDs, up to date they are still few and most of them difficult to find.

On the other hand, it is well known the important differences on the level of practical implementation of the available guidelines among MS, and even among healthcare providers in the same countries. Nevertheless, there is neither a repository of existing CPGs for RDs, nor a systematic procedure to evaluate their real translation into clinical practice that would help to promote those CPGs poorly implemented while ensuring their impact in patients' quality of life.

1.2 Best practices on diagnosis

Undoubtedly, diagnosis is one of the areas most affected by the lack of sufficient scientific and medical knowledge on the RD field. Focussing on rare haematological diseases (RHD), differences in some core lab test for diagnosis have been observed across MS leading to a late diagnosis or even misdiagnosis, especially for the very rare diseases.

Pyruvate Kinase deficiency (PKD) is an example of a chronic RHD in which diagnosis can be delayed for years, can be misdiagnosis or even been labelled as haemolytic anaemia of unknown origin forever.

1.2.1 Pyruvate Kinase Deficiency (PKD)

PKD is a rare autosomal recessive disorder and the most frequent enzymopathy of glycolysis. Currently, 240 different mutations have been identified (www.lovd.nl/pklr). The main clinical symptom of PKD is hemolytic anemia of variable severity, from fully-compensated to life-threatening, transfusion dependent anemia.

As in other RD, real prevalence and number of patients is unknown since there is no patients' registries or exhaustive epidemiological studies. PKD prevalence has been estimated at 1-9:100,000 cases per one hundred thousand people according to ORPHANET. However, based on published literature, estimated PKD prevalence on genetic basis in the general white population was calculated to be 5: 100,000. In addition, there are other reports based on patients' registries with a lower incidence, about 1: 100,000. This discrepancy may be explained by a high number of very mild PKD patients who are not referred to Centres of Expertise, reducing the resulting prevalence. ENERCA (www.enerca.org) enabled a comparison of these numbers and it was concluded that both in The Netherlands and Italy, 2 countries with a large and well-characterized database of patients with PKD, the true frequency was, about 10 times lower than the one estimated on genetic basis 5: 100,000. However, a number of PKD patients are likely to be underdiagnosed and/or misdiagnosis (eg hereditary spherocytosis, thalassaemia major, liver disease) leading to a sub estimation on PKD prevalence. Accordingly, PKD prevalence could be estimated to be 0.25-1: 100,000 for clinical cases.

Different from haemoglobinopathy patients, more prevalent and concentrated by ethnical and/or geographical origin, patients affected by PKD are scarcer and highly distributed. PKD diagnosis is commonly delay due to lack of adequate testing or misinterpretation and no specific drug is still available on the market. Accordingly, PKD patients could benefit for such European approach.

1.2.2 Pitfalls on diagnosis of PKD

Based on ENERCA Reference labs experience on PK activity results from non-expert centres/labs, some pitfalls on PK diagnosis have been observed:

- No correlation between PK activities from non-experts and experts' centres
- RBC package is not separated properly driving to leucocytes presence in the sample and increased PK activity
- PK/HK ratio is not performed in non-expert labs leading to normal results in cases of high number of retyculocytes
- Reference values for PK activity vary according to age and ethnical origin

In addition, there is a number of cases misdiagnosed, the main causes are:

- Hereditary Spherocytosis, it is a more common cause of chronic hemolysis
- Thalassaemia major, in cases of severe blood transfusion anemia
- Liver abnormality, anaemia is considered secondary to the liver disease

Accordingly, there is an urgent need to promote at European level best practices for PKD diagnosis and increase its awareness among medical community; general practicioners, paediatricians and even haematologists.

1.2.3 ERN-EuroBloodNet initiatives to improve PKD diagnosis

Rare Anaemia Disorders European Epidemiological Platform

RADeep, the Rare Anaemia Disorders European Epidemiological Platform, is a joint venture conceived in the core of ERN-EuroBloodNet, the European reference network for rare hematological disorders (www.eurobloodnet.eu), as an umbrella for both new and already existing European patients' registries in rare anaemias.

Ensuring interoperability with European structures fostering research; RADeep will allow mapping at the European level the diagnosis methods, demography, survival rate, main clinical features and treatments of RA patients in order to improve access to specialized and adequate health care and facilitate research and development of new treatments, thus increasing the knowledge and promoting best practices across EU.

RADeep is being implemented in different phases through disease specific arms. For each disease specific arm, a scientific committee will be established including experts on the prevention, diagnosis and clinical care of the disease, researchers, and national coordinators for data gathering. The first phase of implementation of RADeep is being developed for PKD.

Besides mapping PKD patients at the European level, PKDeep goal is also the promotion of best practices for its diagnosis. Indeed, as mentioned before, it is often delayed due to the lack of an adequate testing or their misinterpretation.

Recommendations on PKD diagnosis with the endorsement of ERN-EuroBloodNet

In line with the need of best practice promotion on PKD diagnosis, a global PKD International Working Group was created in 2016 involving 24 experts from 20 Centers of Expertise, aiming to analyse the existing gaps in the PKD diagnosis.

Based on the conduction of a survey on key conflictive points on the diagnosis of PKD and subsequent discussions among members Expert Centers from Europe, USA, and Asia directly involved in diagnosis, a consensous was reached on clinical and technical aspects of PKD diagnosis A high number of ERN-EuroBloodNet experts and members representatives participated in this consensous, as Paola Bianchi, Elisa Fermo, Wilma Barcellini, Tabita Maia, Maria del Mar Mañú Pereira, Eduard van Beers, and Richard van Wijk.

As final result, "Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency" has recently being published by the American Journal of Hematology under the endorsement of ERN-EuroBloodNet, with the objective to help other Centers and professionals to deliver timely and appropriate diagnosis and to increase awareness in PKD.

2- Objectives

One of the key objectives established by ERN-EuroBloodNet is to foster best practice sharing in RHD by creating a comprehensive public repository of reliable evidence based guidelines, ranging from prevention, diagnostic tests and treatments to the organisation of patient-centred management in multidisciplinary teams.

ERN-EuroBloodNet identified as a high priority to a) generate a comprehensive repository of CPGs and the definition of a methodology for their classification based on quality domains (Deliverable 4.1 Report on the comprehensive public database of reliable guidelines) and the assessment of real translation into clinical practice with the final aim to, not only support guideline development when lacking, but also assess their implementation in the different EU Member States.

In this context, the present deliverable aims to:

- Define a plan for establishing the assessment of the holistic clinical management of RHD conditions including prevention, diagnostic tests, treatment and follow up
- Assess the implementation of the Consensus recommendations on the diagnosis of pyruvate kinase deficiency

3- Methods

3.1 Plan for establishing the assessment of the holistic clinical management of RHD conditions including prevention, diagnostic tests, treatment and follow up.

The plan definition and related actions have been undertaken under the umbrella of the ERN-EuroBloodNet Transversal Field of Action (TFA) on best practices, coordinated by Luca Malcovati for the oncological disorders, Achille Iolascon for the non-oncological disorders and Amanda Bok as ePAG representative for bleeding and coagulation disorders, together with the support from the coordination team.

As first step in the assessment process, it was agreed to identify key indicators for the assessment of CPGs awareness and implementation. Since ERN-EuroBloodNet encompasses more than 450 disorders of wide heterogeneity on their clinical coverage and needs, the first actions defined for the identification of:

- Concrete guidelines/recommendations addressing specific disorders which, due to multiple reasons, are expected to be poorly implemented in Member States
- Clinical outcome indicators having some pointing to the minimal requirements (standard of care) and/or related to highly specialized procedures. Indicators should ideally cover several areas as prevention, diagnosis, clinical care and follow up

Accordingly, subnetworks coordinators were requested to coordinate the action on their area of expertise with the support of the ERN-EuroBloodNet Task force for guidelines.

For this task, TFA on best practices coordinators and Coordination team circulated Assessment templates subnetworks-specific, including:

- Objective: To assess at the level of implementation by Member State guidelines/recommendations for a selected disease/condition which due to several reasons (prevalence, cost..) is expected to be poor or not completed implemented.
- Section to indicate Disease/condition selected
- Section to explain why this disease/guideline have been selected for assessment of implementation? (Please, identify the items expected not to be full implemented at the EU-MS level)
- Section to list 5 Clinical outcome indicators

3.2 Assessment of the implementation of the Consensus recommendations on the diagnosis of pyruvate kinase deficiency

The assessment of implementation of the Recommendations for PKD diagnosis is being undertaken in the frame of ERN-EuroBloodNet and RADeep, and in collaboration with UKNEQAS.

The methodological approach for the assessment has been defined based on the identification of centers performing PK diagnosis and their facilities, and a parallel action to establish the External Quality Assessment on PK diagnosis.

3.2.1 Mapping of centers performing PKD diagnosis and facilities for accurate diagnosis and genetic characterization

In order to map European centers performing PKD diagnosis and their facilities a first survey was produced with the objectives to:

- Identify the European medical centres concentrating PKD patients and estimate the number of active PKD patients and with genetic diagnosis
- Identify the European medical centres offering diagnosis facilities for accurate PKD diagnosis and genetic characterization
- Create an up-to-date inventory of medical centres and services available for PKD

The survey included 4 main sections:

a) Organization data
b) Patients' data: Number of PKD patients currently in follow-up, % genotyped, new number of patients per year, participation to any type of patients' registry
c) PKD diagnosis – Part A PK enzyme activity: number of diagnosis tests, method, availability within the medical centre or externalized.
d) PKD diagnosis – Part B *PKLR* genetic analysis: implementation of *PKLR* genetic analysis, availability within the medical centre or externalized.

In addition, authorization for publishing data marked with an * is request before questionnaire submission.

The complete survey is available at the ERN-EuroBloodNet website or in **Annex I Pyruvate Kinase Deficiency survey.**

The survey was implemented through an on-line application within the dedicated section of ERN-EuroBloodNet website, allowing the creation of the up-to-date inventory on medical centres and

diagnosis facilities and the permanent access to the survey in order to update information from already listed centres or add new centres.

The survey was conducted among:

a) The 66 medical centres involved in ERN-EuroBloodNet, already recognized at the European level as centres of expertise in rare hematological diseases. From which, 39 medical centres have been recognized at the national level as centres of expertise in red blood cell disorders and 26 have declared to deal with enzymopathies.

b) Around 40 medical centres not involved in ERN-EuroBloodNet but has previously participate in the ENERCA surveys for membrane and enzyme disorders.

3.2.2 Establishment of the External Quality Assessment on PK diagnosis in collaboration with UKNEQAS

During the 1st year of ERN-EuroBloodNet implementation, a collaboration was established with UKNEQAS for a) the analysis of the state of the art of External Quality Assessment for the RHDs diagnosis and b) promote the establishment of schemes for RHD where gaps are identified.

One of the outcomes from the previous period of implementation was the identification of PK assay as high priority for EQA development given the huge inequalities on its performance across MS.

4- Results

4.1 Diseases and indicators identified for assessment of the holistic clinical management of RHD conditions including prevention, diagnostic tests, treatment and follow up.

The first round of answers gathered a total of 4 selected disorders to assess related guidelines implementation from 3 different subnetworks, specifically concerning to:

- Sickle Cell Disease (SCD) - Red blood cell subnetwork
- HFE- Haemochromatosis - Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork
- Anemia due to genetic disorders of iron metabolism and heam disorders - Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork
- Myelodysplastic syndromes (MDS) - myeloid malignancies subnetwork

Annex II Indicators for guidelines implementation assessment.

In the case of SCD, the rationale for the performance of the assessment is based on the lack of complete implementation of well defined international guidelines for holistic clinical care due to a) budget limitations, b) drug availability, c) lack of disease awareness and/or standard health care policies and d) lack of adequate health professionals training. Indicators have been based on standards of care.

On the contrary, the guideline selected for HFE-Hemochromatosis have been recently published and their implementation can be still poor for this reason.

While for the case of MDS, the indicators selected has been based on the identification of a) several standards of care, b) technique mainstay for diagnosis and risk assessment and c) availability of clinical trials.

It is important to state that additional remarks have been compiled from the Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork to be taken into consideration, as two additional guidelines detected as potentially low implemented. However, the indicators on which base the assessment are still under discussion, and therefore have not been included.

4.2 Assessment of the implementation of the Consensus recommendations on the diagnosis of pyruvate kinase deficiency

4.2.1 Identification of centers performing PK diagnosis and core facilities

A total of 41 medical centres from 10 countries completed the survey. It is important to highlight that answers were received also from two medical centres, one in Bulgaria and one in Cyprus, both of them belonging to ERN-Eurobloodnet as centres of expertise for Red Blood Cell disorders, i.e. haemoglobinopathies. None of them reported any patient affected by PKD or offered any diagnosis facility for PKD. In both cases, *PKLR* gene characterization is offered in the country but not the PK Activity (based on the answers). In addition, in Bulgaria, PKD diagnosis both phenotypic and genetic is not covered by the national health system, thus is not likely to be performed.

Based on the results, a total of 260 PKD patients are currently in follow-up, 231 of them (88,85%) have been genetically characterized. A mean of 25,95 new PKD patients per year would be in follow-up counting all medical centres. Total number of PKD diagnosis is found to be 481, 31,88 new diagnosis per year. Distribution of results on activity by country is shown in Table 1 and Figure 1.

Distribution Patients and diagnosis	Medical Centres	Patients in follow up	Patients Genotyped	% Patients Genotyped	PKD Diagnosis
Belgium	4	8	7	87,50%	21
Czech Republic	1	6	3	50,00%	10
France	5	115	111	96,52%	117
Germany	4	14	14	100,00%	7
Italy	9	42	38	90,48%	133
Netherlands	4	26	23	88,46%	138
Portugal	1	11	11	100,00%	30
Spain	8	20	12	60,00%	22
United Kingdom	2	18	12	66,67%	3
Total	38	260	231	88,85%	481

Table 1. Distribution of activity by country

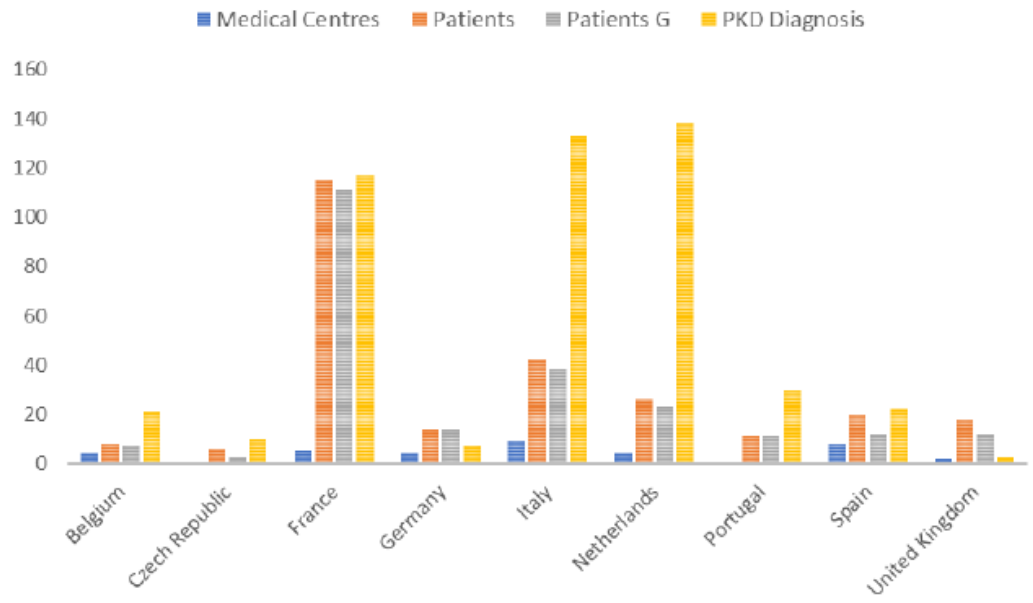


Fig. 1 Distribution of activity by country

Three medical centres are not represented since they do not have any patient in follow-up or have any PKD diagnosis although offering the facilities.

Only seven of the 38 medical centres presented more than 10 patients in follow-up, accounting for 180 of the 260 patients registered and based in France, Italy, Netherlands, Portugal and United Kingdom. However, when adjusting the number of patients in follow-up according to the total population of the country, the highest values are found in France, Netherlands and Portugal, and the lowest in Germany, United Kingdom and Spain.

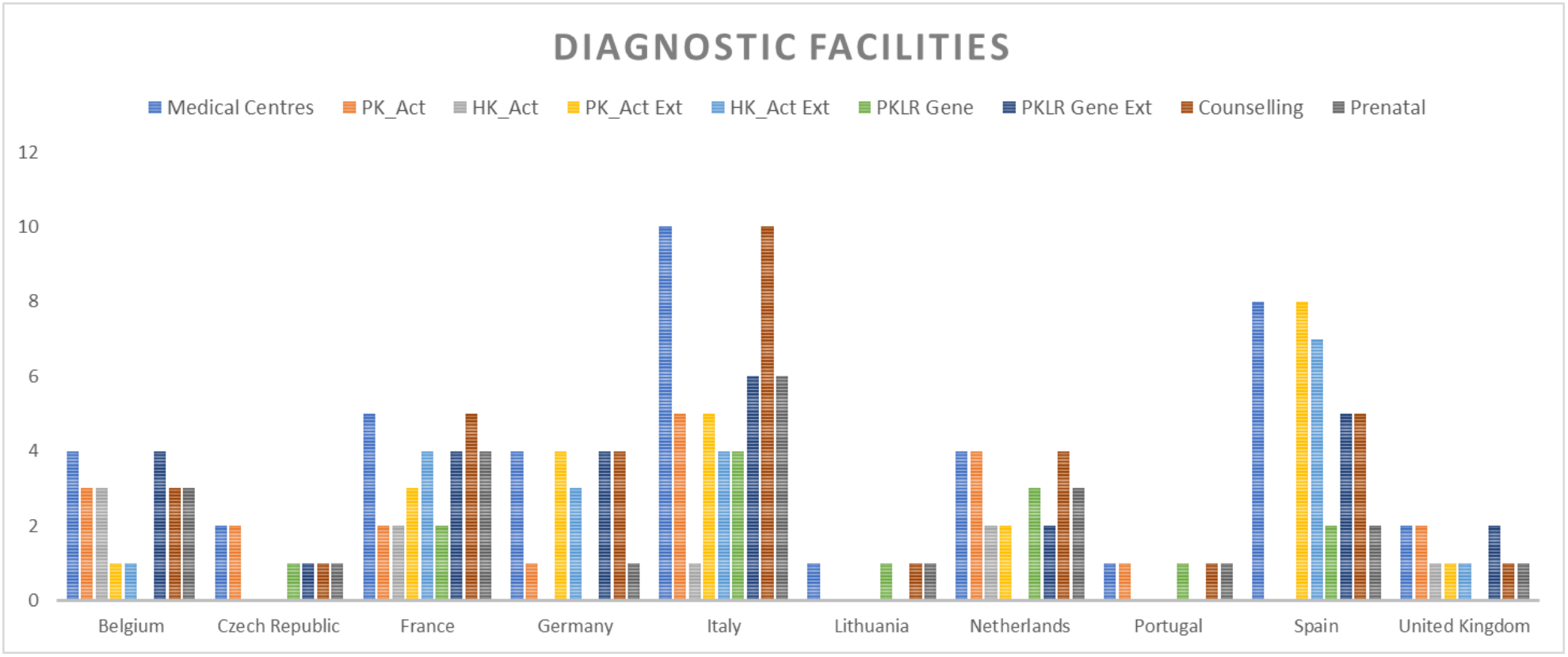
Regarding percentage of PKD patients genotyped, 88,85% of the patients have been genetically characterized. The lowest values for PKD genotyping are found in Czech Republic, United Kingdom and Spain.

Data on diagnostic facilities by country is shown in Table 2 and Figure 2.

Table 2 – Diagnostic facilities by country

Diagnostics facilities	Medical Centres	PK_Act	HK_Act	PK_Act Ext	HK_Act Ext	*PKLR* Gene	*PKLR* Gene Ext	Counselling	Prenatal
Belgium	4	3	3	1	1	0	4	3	3
Czech Republic	2	2	0	0	0	1	1	1	1
France	5	2	2	3	4	2	4	5	4
Germany	4	1	0	4	3	0	4	4	1
Italy	10	5	1	5	4	4	6	10	6
Lithuania	1	0	0	0	0	1	0	1	1
Netherlands	4	4	2	2	0	3	2	4	3
Portugal	1	1	0	0	0	1	0	1	1
Spain	8	0	0	8	7	2	5	5	2
United Kingdom	2	2	1	1	1	0	2	1	1
Total	**41**	**20**	**9**	**24**	**20**	**14**	**28**	**35**	**23**

Figure 2 – Diagnostic facilities by country



Twenty of the 41 medical centres perform PK Activity test in their own centres (48,78%), 4 of them also externalized the PK activity *(further details will be requested)*. Fourteen of them (70,00%) perform PK activity by spectrophotometric assay, reference method by Beutler 1980, 2 of them (10,00) by commercial kit, and in 4 cases specific method was not reported *(further details will be requested)*. In addition, only 9 medical centres perform also HK activity (21,95%) to assess the level of increased PKD activity due to reticulocytosis.

Twenty-four of the medical centres externalize the PK activity (58,54%), 15 of them (62,5%) reported not be informed on the method used by the external laboratory. In addition, 20 medical centres (48,78%) externalize also the HK activity.

To the question "If you do not perform PK activity assay nor in your centre neither externalized please specify the reason:", 4 medical centres answered "We only perform DNA analysis of *PKLR"*. However, 2 of them are likely to be misunderstood the question since they also reported that they performed PK activity. *(further details will be requested)*

To the question "Do you always confirm a decreased PK activity at molecular level?" 34 medical centres answered yes (82,93%), but only 14 centres (34,15%) perform *PKLR* gene analysis.

Thirty-five of the medical centres offers genetic counselling for PKD (85,37%), however only 23 (56,10%) offer prenatal diagnosis.

4.2.2 State of the art of the Establishment of the External Quality Assessment on PK diagnosis in collaboration with UKNEQAS

The External Quality Assessment (EQAs) for PK diagnosis is currently being undertaken in a pilot phase.

First pilot phase involves 9 laboratories from 4 countries (UK – 4 laboratories, Spain – 2 laboratories, Italy – 1 laboratory, Netherlands – 2 laboratories). It has been requested quantitative assay values, with reference range. In addition, also interpretation of results along with the clinical context will be requested to participants.

More laboratories will be included in a second phase during Q1 2019.

5- Impact and next steps

Assessment of the holistic clinical management of RHD conditions including prevention, diagnostic tests, treatment and follow up

The assessment of guidelines awareness and implementation will supply the evidence needed to identify the main causes hampering their transposition into practical level while allowing to centralize efforts for overcome them. eg. Recommendations to working group on education and promotion of their practical transposition among national authorities through the National Contact Points.

Mapping of centers performing PKD diagnosis and facilities for accurate diagnosis and genetic characterization

Identification of centers performing PKD diagnosis and facilities will contribute to a better understanding on the current status of PKD in European countries allowing the facilitation of the access to PKD diagnosis services and promoting the collaboration of the medical centres in the RADeep.

As much important as identifying the medical centres concentrating patients and offering PKD diagnosis facilities is the identification of the GAPs. PKD patients are likely to be undiagnosed and/or misdiagnosed, probably due to the lack of facilities or expertise in a given country. In some countries, most of them are likely to not being genotyped due to economical shortages in the national health systems.

The up-to-date repository of medical centres will enable general practitioners, pediatricians or even hematologists to find experts on the disease to ask for advice and/or request appropriate diagnosis. This will impact in both a reduction of the number of PKD patients non-diagnosed or misdiagnosed and an increase on the number of PKD patients with a genetic diagnosis.

On the other hand, experts on PKD will be able to find colleagues especially in eastern countries to promote collaborative projects on research on PKD physio pathological mechanisms.

The PKD survey has been developed as an on-line application within the dedicated section of ERN-EuroBloodNet website on RADeep allowing the publication of specific data through ERN-EuroBloodNet website to create the up-to-date inventory on medical centres and diagnosis facilities and the permanent access to the survey in order to update information from already listed centres or add new centres.

Access to the survey will be a permanent section in RADeep website allowing new medical centres to join the project.

Establishment of the External Quality Assessment on PK diagnosis in collaboration with UKNEQAS

The foster of new EQAs for diagnosis of those RHDs needing for standardization of procedures across EU will have an impact on the number of cases underdiagnosed or misdiagnosed, allowing the provision of the correct treatment to the patient while contributing to a better epidemiological surveillance of the disease.

Next steps include:

- Continue the gathering the indicators for the assessment of the holistic clinical management of RHD conditions including prevention, diagnostic tests, treatment and follow up: The exercise and discussion on the guidelines selected as well as indicators for the evaluation are still ongoing, accordingly the final list will be provided in the upcoming period of the network.

- Exhaustive mapping diagnosis facilities for accurate PKD diagnosis and genetic characterization – Assessment of the implementation of Recommendations on PKD diagnosis: A second survey is being designed for the gathering of more exhaustive data on how expert centers perform PK diagnosis. The survey is being produced based on key indicators extracted from the "Consensus recommendations on the diagnosis of pyruvate kinase deficiency" that may not be widely implemented in the centers performing diagnosis and in collaboration with UKNEQAS.

- The EQAs for PK assay will be finalized following the participation of laboratories in the second phase foreseen for Q1 2019.

Annex I

Pyruvate Kinase Deficiency survey

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Pyruvate Kinase Deficiency (PKD): Survey on facilities available for diagnosis

***Data that will be published in ERN-EuroBloodNet website under your authorization**

A. Organization Data

Institution*:

Website*:

Department*:

Department e-mail*:

Department phone*:

Contact person*:

Contact person e-mail:

Contact person phone:

Are you a clinician (hematologist, pediatrician)?: Yes/No

Are you a diagnostician (medical doctor, biologist, researcher)?: Yes/No

B. PKD Patients

1. Number of patients affected by PKD currently followed in your centre*:

2. Number of patients affected by PKD currently followed in your centre with genetic diagnosis*:

3. Mean number of new patients per year affected by PKD followed in your centre*:

4. Does your centre participate in a database/registry for PK deficiency?: Yes/No

- If yes:

a. Database/Registry title:

b. If available, link to Database/Registry website:

c. Type of registry:

i. National Registry
ii. International Registry
iii. Regional Registry
iv. Hospital / Laboratory database
v. Other: (Specify)

d. Curator Name:

e. Curator e-mail:

C. PKD Diagnosis - Part A PK enzyme activity

1. Total number of PKD diagnosis*:

2. Mean number of new PKD diagnosis per year*:

3. Do you perform in your centre PK activity assay?*:Yes/No

- If yes:

a. Which method do you use to perform PK activity assay:*

i. Spectrophotometric assay (Beuter 1980)
ii. Other quantitative methods (please specify):
iii. Semi-quantitative methods (please specify):
iv. Commercial kit (please specify):
v. Other (please specify):

b. Do you also perform hexokinase (HK) enzyme activity to assess mean red cell age through PK/HK ratio?: Yes/No

4. Do you externalyze the PK activity quantitative assay?*: Yes/No

- If yes:

a. External Institution/Laboratory Name (Not mandatory):

b. Which method is used to perform PK activity assay: Multiple choice

i. Spectrophotometric assay (Beuter 1980)
ii. Other quantitative methods (please specify):
iii. Semi-quantitative methods (please specify):
iv. o Commercial kit (please specify):
v. o Other (please specify):
vi. I am not informed

b. Do you also externalyze hexokinase (HK) enzyme activity to assess mean red cell age through PK/HK ratio? Yes/No

5. If you do not perform PK activity assay nor in your centre neither externalized please specify the reason:

a. We only perform DNA analysis of PKLR
b. PK activity test is not authorized in my centre to be externalized
c. PK activity assay is not available in my country (to the best of my knowledge)
d. Other (Please, specify):

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D. PKD Diagnosis - Part B PKLR genetic analysis

1. Do you always confirm a decreased PK activity at molecular level?: Yes/No

   If not always, please specify in which cases:

2. Do you perform in your centre PKLR genetic characterization?*: Yes/No

   If yes:

   a. Which method is used for PKLR genetic characterization*
      i. Sanger
      ii. NGS
      iii. Other (please specify):

3. Do you externalyze the PKLR genetic characterization?*: Yes/No

   If yes:

   a. External Institution/Laboratory Name (Not mandatory):
   b. Which method is used for PKLR genetic characterization:
      iv. Sanger
      v. NGS
      vi. Other (please specify):
      vii. I am not informed

E. Genetic counselling and prenatal diagnosis

1. Genetic counselling for PKD is offered in your centre*?: Yes/No

2. Is prenatal diagnosis for PKD available in your centre*? Yes/No

Do you give your consent to publish data with* in the ERN-EuroBloodNet website www.eurobloodnet.eu ? Yes/No

Annex II

Indicators for guidelines implementation assessment

Disease/condition selected	**Sickle Cell Disease**	**HFE-hemochromatosis**	**Anemia due to genetic disorders of iron metabolism and heam disorders**	**Myelodysplastic syndromes**
Guideline/ Recommendation	Nr. 10 RBC: Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014 Nr. 11 RBC: ENERCA clinical recommendations for disease management and prevention of complications of sickle cell disease in children	Nr. 9. HH-iron: Key-interventions derived from three evidence based guidelines for management and follow-up of patients with HFE haemochromatosisHaemochromatosis working group. BMC Health Serv Res. 2016 Oct 13;16(1):573.	Nr. 7 HH-Iron: Practice guidelines for the diagnosis and management of microcytic anemias due to genetic disorders of iron metabolism or heme synthesis. Blood 2014	Nr. 1 Myeloid: Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013 Oct 24;122(17):2943-64
Why this disease/guideline have been selected for assessment of implementation? (Please, identify the items expected not to be full implemented at the EU-MS level)	SCD is a chronic condition which health burden is increasing due to better care leading to improve global survival and to global movements. Although international guidelines exist for its holistic clinical care they are not completely implemented across EU due to a) budget limitations, b) drug availability, c) lack of disease awareness and/or standard health care policies and d) lack of adequate health professionals training.	Key interventions for HFE -hemochromatosis have been developed and published by a tem from Belgium and the Netherlands. Outcome parameters need to be discussed in ERN team; evidence based guidelines and clinical outcome parameters for the more rare forms of HH need to be developed and discussed	Currently the only evidende based guidelines on the topic; guideline developed by a multidisciplinary team of Dutch (only) professionals from different hospitals in the Netherlands. More specific and SMART defined outcome parameters should be defined and discussed for all 14 diseases of the guideline.	Cytogenetic analysis represents a mainstay for diagnosis and risk assessment and should be available for any patient with MDS. Erythropoiesis stimulating agents, lenalidomide, azacititine and allogeneic stem cell transplantation are the standard of care for patients with MDS. In highly specialized centers, somatic mutation analysis through NGS and clinical trials should be available.
Clinical outcome indicators: It would be preferable to have some pointing to the minimal requirements (standard of care) and 1 or 2 related to highly specialized procedures. Indicators should idealy cover several areas	1. Newborn screening	1. Screening of first degree relatives of patients	1. Diagnosis within 6 months after presentation	1. Cytogenetic analysis
	2. Vaccination (meningococcus, streptococcus pneumoniae, capsulated cocci)	2. HFE-gene testing when both TSAT and ferritin are increased	2. Screening of family members	2. Erythropoiesis stimulating agents for lower risk MDS
	3. Antibiotic prophilaxis until 5 ye at least	3. Phlebotomise (bi) weekly when ferritin are increased to target ferritin between 50 and 100 ug/l. Iron parameters patients should be monitored and re-accumulation should be prevented	3. Timely start of treatment	3. Lenalidomide for lower risk MDS with del 5q
	4. Transcranial Doppler starting at 2 ye	4. Patients with suspected overlaod should undergo TSAT and ferritin testing, and only HFE testing when TSAT is increased		4. Azacitidine for high risk MDS
	5. Availability of Hydroxyurea treatment	5. Before phlebotomy patients should be screened for end organ damage (liver, heart, endocrine organs, joints)		5. Allogeneic stem cell transplantation for high risk MDS
				6. Mutation analysis by next generation sequencing
				7. Access to clinical trials